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(54) Title: POKEWEED ANTIVIRAL PROTEIN POLYPEPTIDES WITH ANTIVIRAL ACTIVITY

(57) Abstract: A molecular model of pokeweed antiviral protein (PAP)-RNA interactions was used to rationally engineer FLP-102 (^{151}AA^{152}) and FLP-105 (^{191}AG^{192}) as nontoxic PAP proteins with potent anti-HIV activity. FLP-102 and FLP-105 have been produced in *E. coli* and tested both *in vitro* as well as *in vivo*. These proteins depurinate HIV-1 RNA much better than ribosomal RNA and are more potent anti-HIV agents than native PAP or recombinant wild-type PAP. They are substantially less toxic than native PAP in BALB/c mice and exhibit potent *in vivo* activity against genotypically and phenotypically NRTI-resistant HIV-1 in a surrogate Hu-PBL-SLID mouse model of human AIDS. Rationally engineered nontoxic recombinant PAP proteins such as FLP-102 and FLP-105 may provide the basis for effective salvage therapies for patients harboring highly drug resistant strains of HIV-1. The documented *in vitro* potency of FLP-102 and FLP-105, their *in vivo* antiretroviral activity in HIV-infected Hu-PBL SCID mice, and their favorable toxicity profile in BALB/c mice warrant the further development of these promising new biotherapeutic agents.